Claim 48 has been amended, and the amendment is also effective as to all of Claims 49-62, which depend from Claim 48. Applicant believes that the Amendment is responsive to the rejection under Section 112 and makes that rejection moot.

The second paragraph of the Action states that Jones et al. generically discloses the present invention at column 2, and specifically discloses the pyrrolidino analog at column 39. The Examiner says that a side-by-side comparison of the present invention with the pyrrolidino compound is necessary to rebut the allegedly strong presumption of obviousness established by the patent.

Applicant submits herewith five Declarations which report the biological effects of the present invention, compared to the prior pyrrolidine compound. The Declarations speak for themselves, but some explanation will be given. First, however Applicant will point out the legal situation which allows him to present efficacy data proving the patentability of the present invention.

As the Examiner pointed out, the piperidino compound of the present invention is included in the very broad generic disclosure of Jones et al., but is not specifically taught there. Thus, the invention is much in the situation of the invention which was considered in Ex parte Strobel, 160 U.S.P.Q. 352 (P.O. Bd. App. 1968). While the invention is generically included in a huge genus, nothing in Jones et al. particularly points to the present invention among the many possible combinations in the disclosure.

Parenthetically, Applicant points out that the present invention consists of a single compound, the physiologically acceptable esters and ethers which can be formed on that compound's

two hydroxy groups by conventional chemical means, and the physiologically acceptable acid addition salts thereof. Pharmaceutical methods making use of the compound's remarkable activities, and pharmaceutical compositions embodying the compound, are also claimed.

Thus, cases such as Strobel, which stem from the general patent law doctrine that an applicant may select a particularly advantageous narrow invention from a broad prior genus which does not particularly point to his narrow invention, give the principle of patentability upon which Applicant rests his case.

The principle of In re Papesch, 315 F.2d 381, 137 U.S.P.Q. 43 (1963), allows presentation of biological efficacy data to show the patentable distinction of an invention over prior compounds. Papesch, and the many cases which follow it, say that the patentability of an invention is to be judged by consideration of all of its properties, and not merely on the basis of its structure. Its properties include its biological or pharmaceutical activities. Thus, an applicant may present evidence of the unexpected benefit of his compound, compared to the activity of a prior compound, to show that the invention as a whole, including its properties, is unexpected.

Accordingly, Applicant submits herewith a group of five Declarations by experts in the biological properties of anti-estrogens and antiandrogens. The Declarations show that the present invention, considered as a whole, is most unexpectedly superior to the corresponding pyrrolidino compound named at column 39 of Jones et al.

The Declarations report substantially all of the experimentation which has been done on the two compounds. As the various Declarations explain, some tests have not been

reported because they did not provide sound comparisons. For example, Mr. Black does not report some experiments in which a given salt of one compound or the other was used, because the corresponding salt of the other compound was never tested. Dr. Clemens reports only the single anti-tumor test in which both compounds were tested side-by-side, and does not report tests of only one compound, because his experience is that the test is not reproducible enough to compare the results of different tests.

As Mr. Black explains in the introduction of his Declaration, the pyrrolidino compound was tested many times to confirm its efficacy, because it was the first antiestrogen compound having very low estrogenic activity in itself. The compound of the present invention has been tested in fewer tests, because it is newer, and also because it was unnecessary to prove again that such a compound can exist. It was tested only sufficiently to prove that it was superior to the pyrrolidino compound.

No clinical or human testing of the compounds is presented. The compound of the present invention is now being tested in humans in Phase I or pre-clinical testing. It appears that no such testing of the pyrrolidino compound will ever be carried out.

Applicant invites the Examiner's close study of the enclosed Declarations. It is believed that the data in the Declarations, and the conclusions of the expert Declarants, speak for themselves, and Applicant will here present only the briefest summary of the Declarations. Applicant offers, however, to provide one or more of the Declarants for an interview with the Examiner, if such an interview would be of value.

Declaration of Larry J. Black

Mr. Black is responsible for the fundamental antiestrogen testing in the laboratories to which Applicant belongs, and has carried out a great many tests of the estrogenic and antiestrogenic properties of the compounds in standardized laboratory animals.

The basic tests used by Mr. Black are the uterotropic and antiuterotropic tests, wherein the compound to be tested is administered to an immature or ovariectomized female rat or mouse and the growth response of the uterus is measured and compared to the response caused by estradiol. In antiuterotropic tests, both estradiol and the compound are administered to determine if the compound can prevent the response caused by estradiol.

Mr. Black concludes from his study of many tests that the present compound is a more effective antiestrogen, and is less estrogenic in itself, than is the pyrrolidine. He says that he believes that the optimal antiestrogenic performance of the present compound is the control of almost 90% of the effect of estradiol, while the optimal performance of the pyrrolidine is about 75% control. Further, he concludes that the present compound is effective at very much lower doses than the pyrrolidine.

Mr. Black says that neither compound has much uterotropic activity, but that the maximum response of the pyrrolidine is clearly greater than that of the present compound, under any test conditions, indicating the greater estrogenicity of the pyrrolidine.

One of the most remarkable differences between the compounds is demonstrated by Mr. Black's duration of action tests.

It took 20 days for the uterine response to estrogen to recover fully after administering the pyrrolidine, but the response did not fully recover until 90 days after administering the present compound. This is a very significant difference.

The relative binding affinity tests in rat tissue also show a very substantial difference in favor of the present compound. Mr. Black reports that the pyrrolidine has affinity, at 30°, 1.15 times that of estradiol, while the present compound's affinity is 2.9 times that of estradiol. Clearly, the present invention is much more likely to exclude estradiol than is the pyrrolidine.

Mr. Black reports that only a few RBA tests in mouse tissue have been done, and do not allow firm conclusions.

Mr. Black reports a group of dissociation tests, but explains in detail that the tests do not give a basis for comparison of the two compounds.

Regression tests were done to determine the compounds' ability to regress uterine hypertrophy when the compounds were administered after hypertrophy was established. Mr. Black points out that the present compound regressed the estrogen response closer to the no-treatment level than did the pyrrolidine.

Blockade tests were carried out to determine the compounds' ability to prevent the uterotropic effect when administered before an estrogenic agent. Mr. Black concludes that the present compound completely blocks response from later estradiol treatment, while the pyrrolidine allowed some hypertrophy. The animals treated with the pyrrolidine followed by tamoxifen plus pyrrolidine exhibited the full estrogenic response of tamoxifen, in Mr. Black's opinion, while those treated with tamoxifen plus

the invention showed a lesser degree of hypertrophy.

Mr. Black also reports tests of older compounds, naphthalenes of U. S. Patent 4,230,862, which was cited in the parent of the present application. The compounds have acyl side chains similar to that of the present compound; one has a piperidino side chain and the other a pyrrolidine. Mr. Black concludes from his uterotropic and antiuterotropic tests that the piperidino naphthalene is more antiuterotropic and less uterotropic than the pyrrolidino naphthalene.

He also carried out relative binding affinity tests on naphthalenes, which tests were not conclusive. Tests of the methanesulfonates indicate the pyrrolidine is more effective, but tests of the citrates indicate that the piperidine is more effective.

Declaration of James A. Clemens, Ph.D.

Dr. Clemens carried out a single test in which both the compound of this invention and the pyrrolidino compound were tested side-by-side for their ability to reduce or inhibit the growth of a standard laboratory tumor induced in rats by 7,12-dimethylbenzanthracene. The results of that test, according to Dr. Clemens' conclusion, show that the effect of the pyrrolidino compound was probably not different from the results in the control animals, and that the compound of this invention provided useful regression of the estrogen-dependent tumors.

Declaration of Michael L. Hanlin

Mr. Hanlin is responsible for the testing of antiandrogens and potential antiandrogenic agents in the laboratories to which Applicant belongs. In his Declaration, he concludes that neither the compound of the present invention nor the pyrrolidino compound

has substantial affinity for binding to prostatic androgen receptors. However, when the compounds were administered to animals and the effects on accessory sex organs were observed, a difference between the compounds was seen. Mr. Hanlin observes that the piperidino compound inhibits weight gain of the seminal vesicles and ventral prostates when administered with testosterone propionate, whereas the pyrrolidino compound allowed weight gains of those organs approximately equal to treatment with testosterone propionate alone. Mr. Hanlin concludes that the compound of this invention is a potent antiandrogen, but that the pyrrolidino compound of Jones et al. appears to be devoid of antiandrogenic activity.

Declaration of James H. Clark, Ph.D.

Dr. Clark is a professor at Baylor School of Medicine, and is an extremely well-known authority on the physiology of steroids and hormones. He is a consultant for the laboratories to which Applicant belongs.

Dr. Clark reports that he has studied tissues and sections of tissues from the uteri of animals used in Mr. Black's experiments. He presents photomicrographs of representative tissues from animals treated in various ways with estradiol, the compound of this invention and the pyrrolidino compound of Jones et al. He concludes that the major difference between the Jones et al. compound and the present invention is the very low to non-existent estrogenicity of the present compound as compared to the pyrrolidino compound. In the Declaration, Dr. Clark compares various pairs of photomicrographs as showing comparisons between the compounds. Here, Applicant will only point to Dr. Clark's Exhibits 5 and 6, where the animals were treated only with the